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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/715,283	11/17/2003	Erwin Bischoff	LeA 34750 D1	5224

35969 7590 05/21/2004

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EXAMINER	
PATEL, SUDHAKER B	
ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 05/21/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/715,283	BISCHOFF ET AL.	
	Examiner	Art Unit	
	Sudhaker B. Patel, D.Sc.Tech.	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 17 November 2003.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-17 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-17 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 09/943,325.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicants' communication paper dated 11/27/03 is acknowledged.
The claims in this application are the claims 1-17.
First action on merits follows.

Priority

1. Applicant is reminded that in order for a patent issuing on the instant application to obtain the benefit of priority based on priority papers filed in parent Application No. 09943325, filed 8/30/2001, now U.S.P. 6649616 under 35 U.S.C. 119(a)-(d) or (f), a claim for such foreign priority must be made in this application. In making such claim, applicant may simply identify the application containing the priority papers.

Double Patenting

2. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

3. Claims 1-17 are rejected under the judicially created doctrine of double patenting over claims1-16 of U. S. Patent No. 6649616 since the claims, if allowed, would improperly extend the "right to exclude" already granted in the patent.

The subject matter claimed in the instant application is fully disclosed in the patent and is covered by the patent since the patent and the application are claiming common subject matter, as follows: Instant claims1-8 related to **compounds** overlap with the ref.'616 claims 1-8(see columns 96-103). Instant **process** claim 9,10 overlap with ref.'616 claims 11,12(see columns 106,107). Instant claim 12 overlap with ref.'616 claim 10(see column 104). Instant composition/medicament and use claims 13-17 overlap with ref.'616 claims 13-16(see column 108).

The instant claims differ from the ref.'616 claims in that the instant invention includes a brooder scope of invention in claim 1 for variables D and A respectively.

4. Therefore, if instant claims were allowed, it would improperly extend the "right to exclude" already granted in the patent.

Furthermore, there is no apparent reason why applicant was prevented from presenting claims corresponding to those of the instant application during prosecution of the application, which matured into a patent. See *In re Schneller*, 397 F.2d 350, 158 USPQ 210 (CCPA 1968). See also MPEP § 804.

Claim Rejections - 35 USC § 101

5. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

6. Claims16, 17 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a process or a definite step asserted utility or a well-established utility.

The claims are related to method of use of compounds of claims 1-15 which do not exactly and definitely describe: 1). Preparation/process of making medicaments, and 2). A process of step of administration for treating and/or prevention of a disease.

Claims 12,13 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a step or process of making a medicament and step of administration, asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims1-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(A). Claim1-13 recite compounds of the Formula (where applicable). Correction to:" A compound of Formula or A compound of claim 1 " is required.

(B). Claims 1-12 recite:" A compound of the Formula (where applicable) and their salts, hydrates, hydrates of salts and solvates". Corrections to:" A compound of the Formula (where applicable) or pharmaceutically acceptable salts or hydrates or solvates thereof" is required.

(C) . Claim 13 recites:" compounds as defined in any of the preceding claims for controlling diseases". Claim remains silent about the exact nature of a disease. Also0, any of the preceding claims includes the intermediates used for the synthesis of the compounds. Therefore, it is not very clear as to what is exactly included in this claim.

(D). Claims 14,15 are related to medicaments. Usually, a pharmaceutical composition claim is recited as:" A pharmaceutical composition comprising of a compound of claim 1 and a pharmaceutically acceptable carrier". Correction is required.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 16,17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a single, exact and definite disease for a treatment, does not reasonably provide enablement for the prevention and /or treatment of all of the peripheral and cardiovascular disorders. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use/ practice the invention commensurate in scope with these claims. .

The claims include 1). Method(s) of preparation of medicaments as well as 2). Method of prevention and/or treating ischemic disorders of the cardiovascular system which include (but not limited to coronary heart disease, stable & unstable angina pectoris, of peripheral and arterial occlusive diseases, of thrombic vascular occlusions, of myocardial infrarction and of reperfusion damage, and the diseases yet to be discovered.

In cases directed to chemical compounds, which are being used for their physiological/biological activity, the scope of the claims must have a reasonable correlation to the scope of enablement provided by the specification. See in re Surrey 151 USPQ 724 regarding sufficiency of disclosure for a Markush group and In re Wiggins 179 USPQ 421.

"Compounds, or pharmaceutically acceptable salts or hydrates or solvates, and pharmaceutical composition(s) thereof as recited in the claims read on all such moieties regardless of complexity of structure and point of attachment to the aliphatic or carboxylic or aromatic or heterocyclic core or bridge/chain for which there is no sufficient teaching how to make and how to use at any one selective location among the many possible sites present. The situation is more confusing when a skilled person in the art tries to visualize the multiple possibilities of combining a compound of claim 1(or claims dependent on it) and/ or its pharmaceutical composition for treating a patient having diseases or conditions associated with method of prevention and/or treating ischemic disorders of the cardiovascular system which include (but not limited to coronary heart disease, stable & unstable angina pectoris, of peripheral and arterial occlusive diseases, of thrombic vascular occlusions, of myocardial infrarction and of reperfusion damage, and diseases yet to be discovered in general.

Applicants provide no reasonable assurance that any and all derivatives of the instant compounds and their compositions as outlined, will have ability to generate the compounds in vivo or in vitro by one or more processes.

In evaluating the enablement question, several factors are to be considered. In re Wands, 8 USPQ 2d 1400 (Fed. Cir. 1988); Ex parte Forman, 230 USPQ 546. The factors include:***(1).*** The nature of invention;***(2).*** the state of prior art ;***(3).*** the predictability or lack thereof in the art; ***(4).*** the amount of direction or guidance present;***(5).*** the presence or absence of working examples;***(6).*** the breadth of the claims, and ***(7).*** the quantity of experimentation needed.

The nature of the invention:

The compounds and their method of use claim(s) are drawn for treatment and/or prevention of any disorder of peripheral and cardiovascular diseases in a generic way. The claims remain silent about to whom the same is to be given.

The state of prior art:

The state of prior art is that there is no one compound that is capable of the treatment or prevention of the disorders in a mammal. There are many factors to consider for the treatment or prevention of disorders such as the inhibition or activation of different receptors, the internal environment of the cell and how certain compounds will mediate different pathways.

The predictability or lack thereof in the art:

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. In re Fisher, 427 F. 2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statue. In the instant case, the instantly claimed invention is highly unpredictable since one skilled in the art would recognized that in regards to therapeutic and preventive effects on any disorder or condition in a mammal which will include a human being is dependent on many conditions such as the chemical pathways present, what receptors are inhibited or activated and what the internal environment of the cell is.

Hence, in the absence of a showing of correlation between the treatment or/and prevention of ischemic disorder(s) of the cardiovascular system with the inhibition of adenosine uptake on the treatment of ischemic disorder of the cardiovascular system, one skilled in the art is unable to fully predict possible results from the ad ministration of the compounds, salts, solvated, medicaments thereof as claimed herein.

The nature o pharmaceutical arts is that IT INVOLVES SCREENING IN VITRO AND VIVO TO DETERMINE WHICH COMPOUNDS EXHIBIT THE DESIRED PHARMACOLOGICAL ACTIVITIES. There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art is limited.

Specification on pages 39-44 recites various test(s) and assay methods for binding activity of adenosine receptors in rabbit erythrocytes. Results recited/summarized in lines 29-31 in page 40 state that:" Using this test, the IC50 value determined for Example 1-1 was 30nM, that for Example 1-3 was 20 nM, that for Example 1-14 was 30 nM, that for Example 1-33 was 40nM, that for Example 2-1 was 20nM and that for Example 2-18 was 20nM.

These results will only serve for the preliminary screening of many compounds, and not for treating the diseases as claimed herein.

The facts as provided above do support the need for additional quantity of experimentation which would be an undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan, regarding the

method of treatment for various disorders/conditions related to inflammation, cancer, and other diseases.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the use of instant compounds to treat various disorders/diseases related to MMPs.

10. When the best efforts have failed to achieve a goal, it is reasonable for the PTO to require evidence that such a goal has been accomplished, *In re Ferens*, 163 USPQ 609. The failure of skilled scientists to achieve a goal is substantial evidence that achieving such a goal is beyond the skill of practitioners in that art, *Genentech vs. Novo Nordisk*, 42 USPQ2nd 1001, 1006.

Conclusion
Allowable Subject Matter

10. Claims 1-12 related to compounds and their synthesis would be allowable if rewritten to overcome the rejection(s) under 35 U.S.C. 112, second paragraph and other rejections, set forth in this Office action and to include all of the limitations of the base claim and any intervening claims.

11. Claim 14 related to a pharmaceutical composition would be also considered for allowance it redrafted as recited in the parent case.

12. Claim 16 related to method of treating claim would be considered for allowance if represented as in the parent case.

13. The following is a statement of reasons for the indication of allowable subject matter: The closest prior art ref. Mueller et al (U.S.P. 5607962 dated 3/1997) teaches making of compounds with a core:" phenyl substituted indole-CH2-Phenyl-cyclohexane-CO-NH-CH(Phenyl)-CO-NH2".

14. The ref. '962 differs from the instantly claimed compounds by not having a bridge: -R1-CO-A—attached to D variable".

15. The reference '962 does not indicate or suggest to arriving ate the instant compounds.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sudhaker B. Patel, D.Sc.Tech. whose telephone number is (571) 272-0671.

The examiner can normally be reached on 6:30 to 5:00 pm (Monday-Thursday). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Mukund J. Shah can be reached on (571) 272 0674 or Sr. Examiner Mr. Richard Raymond at (571) 272 0673 or Mr. James O. Wilson at (571) 272-0661.

The fax phone numbers for the organization where this application or proceeding is assigned are 703 308 4556 for regular communications and 703 308 4556 for After Final communications. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703 308 1235.Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through

Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Sudhaker B. Patel, D.Sc. Tech.
May 10, 2004

RICHARD L. RAYMOND
PRIMARY EXAMINER

MUKUND SHAH
SUPERVISORY PATENT EXAMINER
ART UNIT 1624/1623